

Artificial Nucleases as Antiviral, Antibacterial Agents

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Objective and Approach

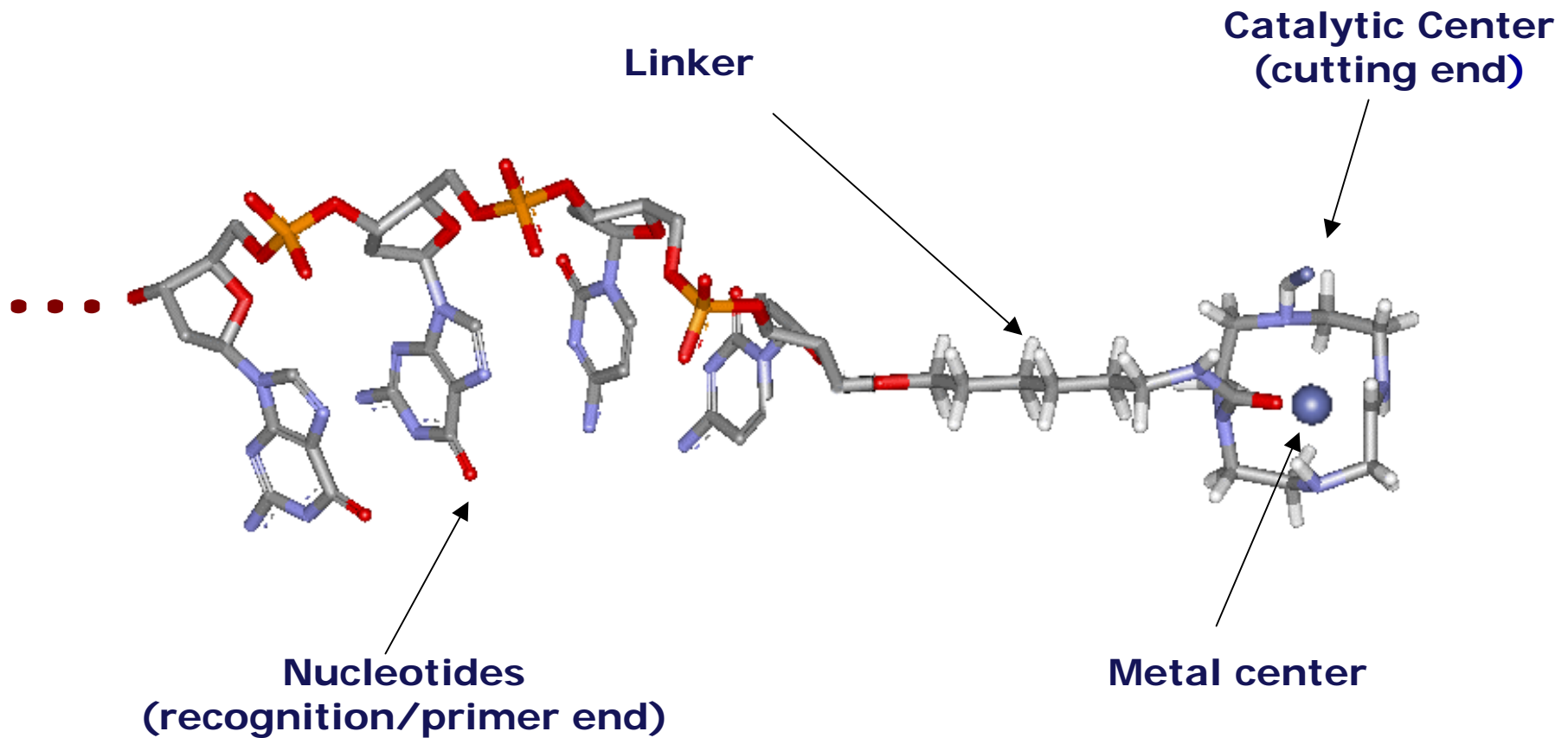
Objective

Develop strongly binding artificial nucleases, with enhanced sequence-recognition and stability for anti-bacterial and anti-viral applications.

Approach

Synthesize small metal-chelator complexes suitably modified for coupling to oligonucleotides (ODN) as nuclease-like probes for binding to target viral RNA sequences.

Anatomy of an Artificial Nuclease



Antisense as Paradigm for Development

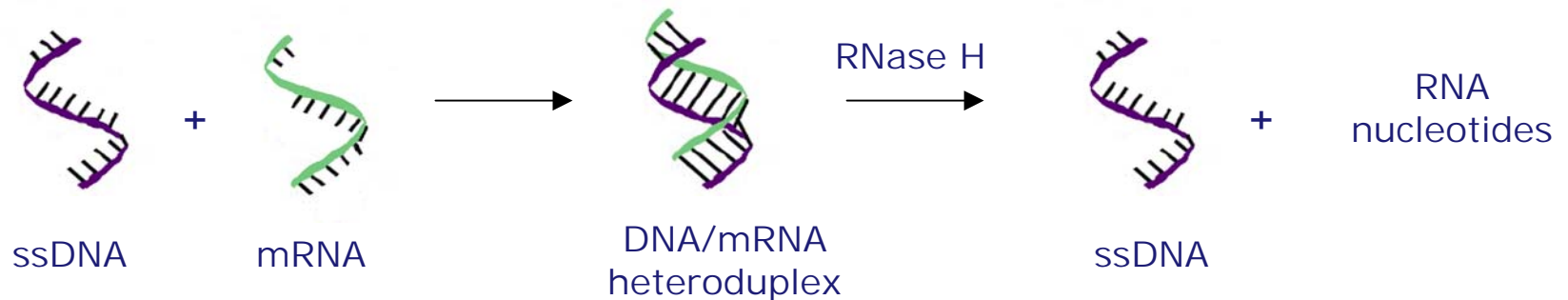
Antisense Pathways:

-Steric Blockade: Through complementary pairing of probe to target sequence.

Problem: only effective from 5' end to translational start site.

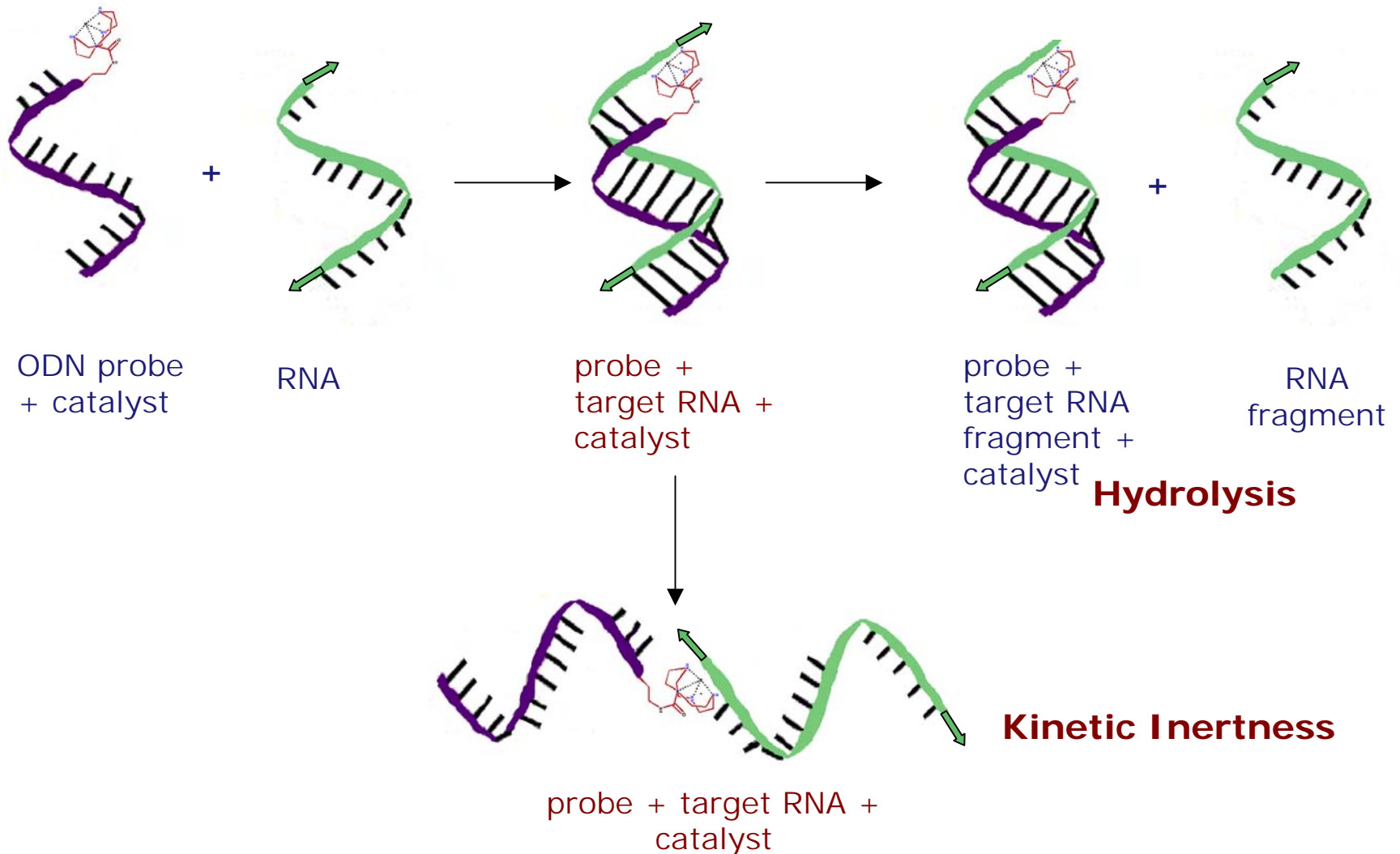
-RNAase H Catalysis: DNA-dependent hydrolysis of RNA target.

Problem: issues with turning on RNase.



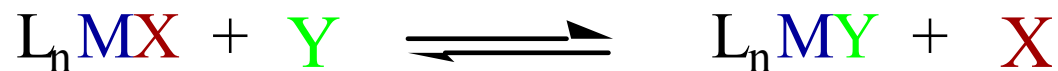
Hybrid Approach: Both Steric and Hydrolytic

High Sequence-Specificity



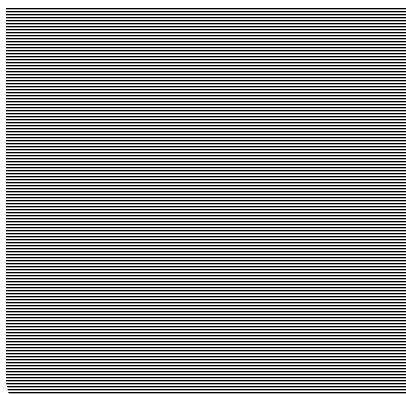
Kinetic Inertness

Substitutional Inertness



X, Y = ligands

exchange of ligands coordinated to the central ion, M, is very slow.



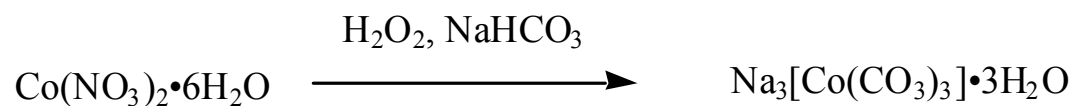
Example" Co(III) coordinated to tetra-dentate chelator.

Using Inertness as Steric Blockade

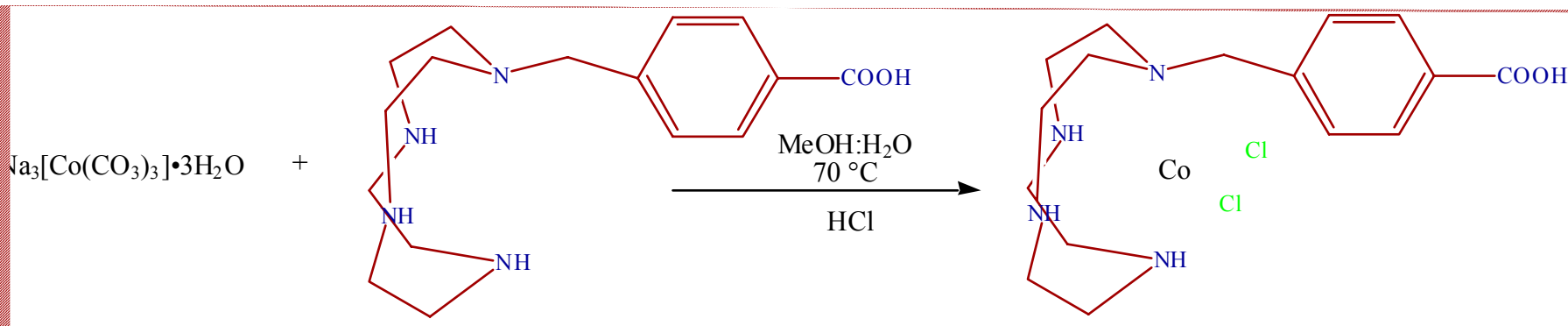


Incorporating Co(III)

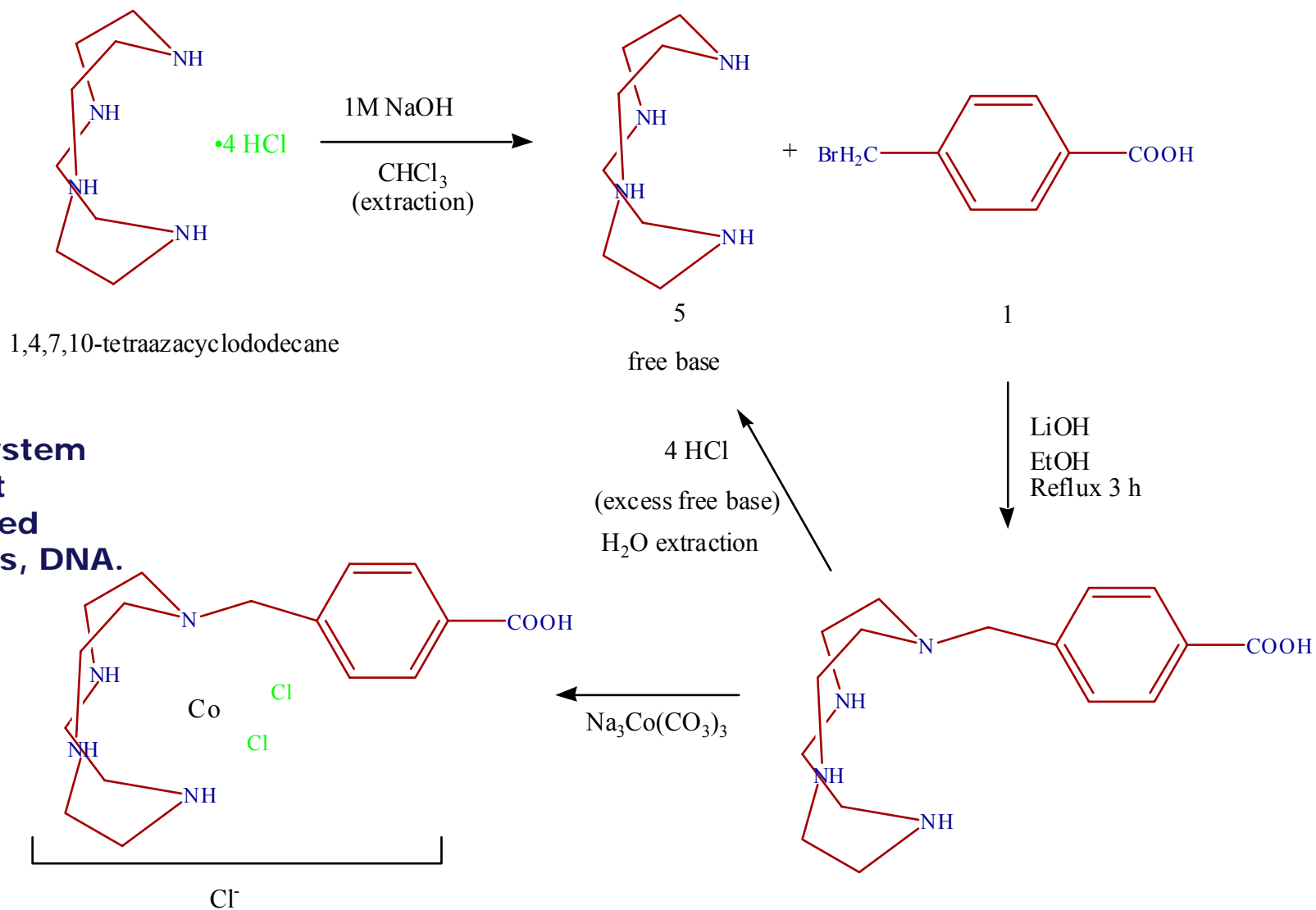
Convert Co(II) to Co(III)



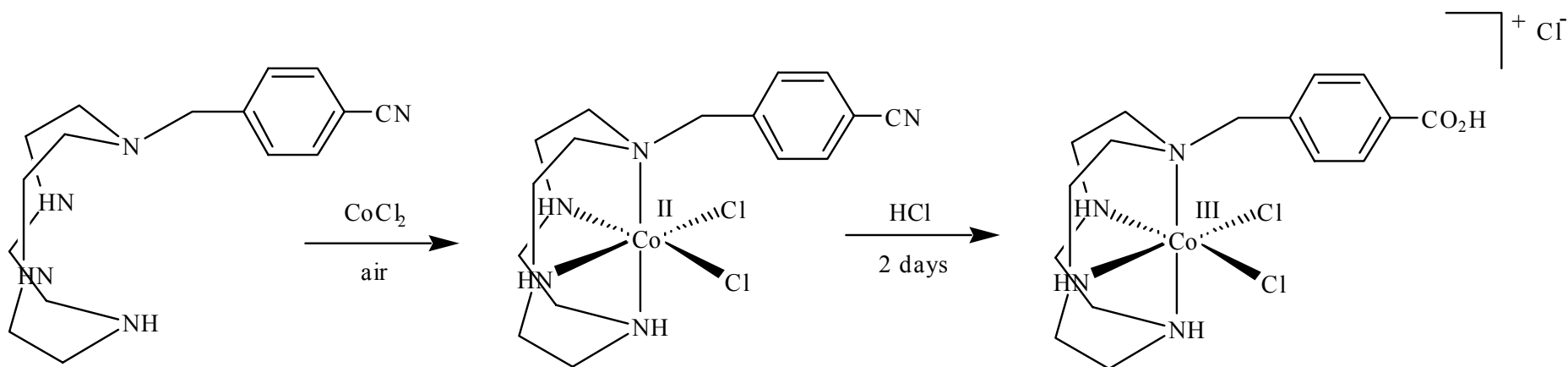
Transfer to Cyclen-mba



Functionalizing Cyclen



Alternative Synthesis



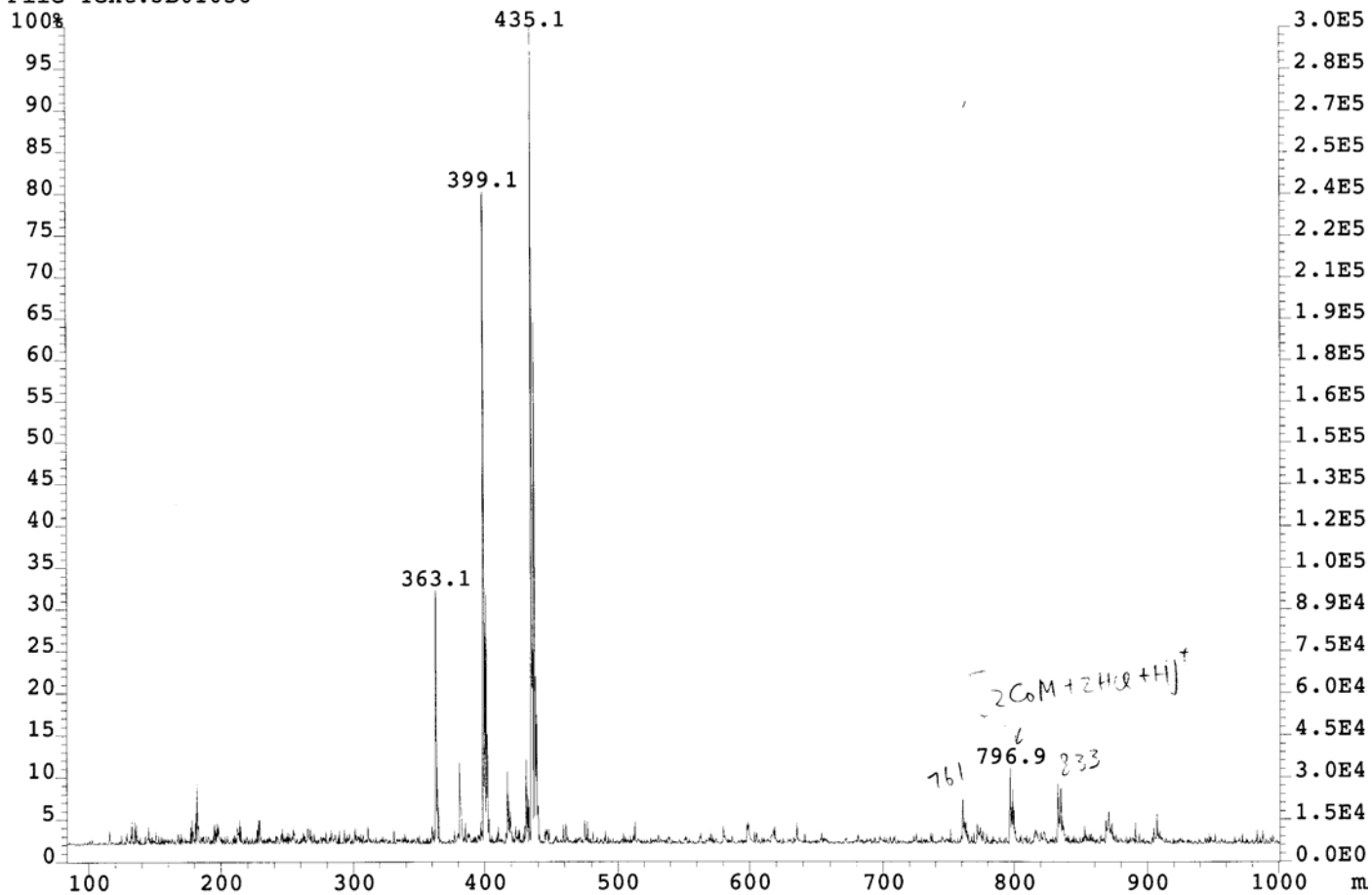
violet crystals

IR Spectrum of $[\text{CoCl}_2(\text{cycmba})]\text{Cl}$

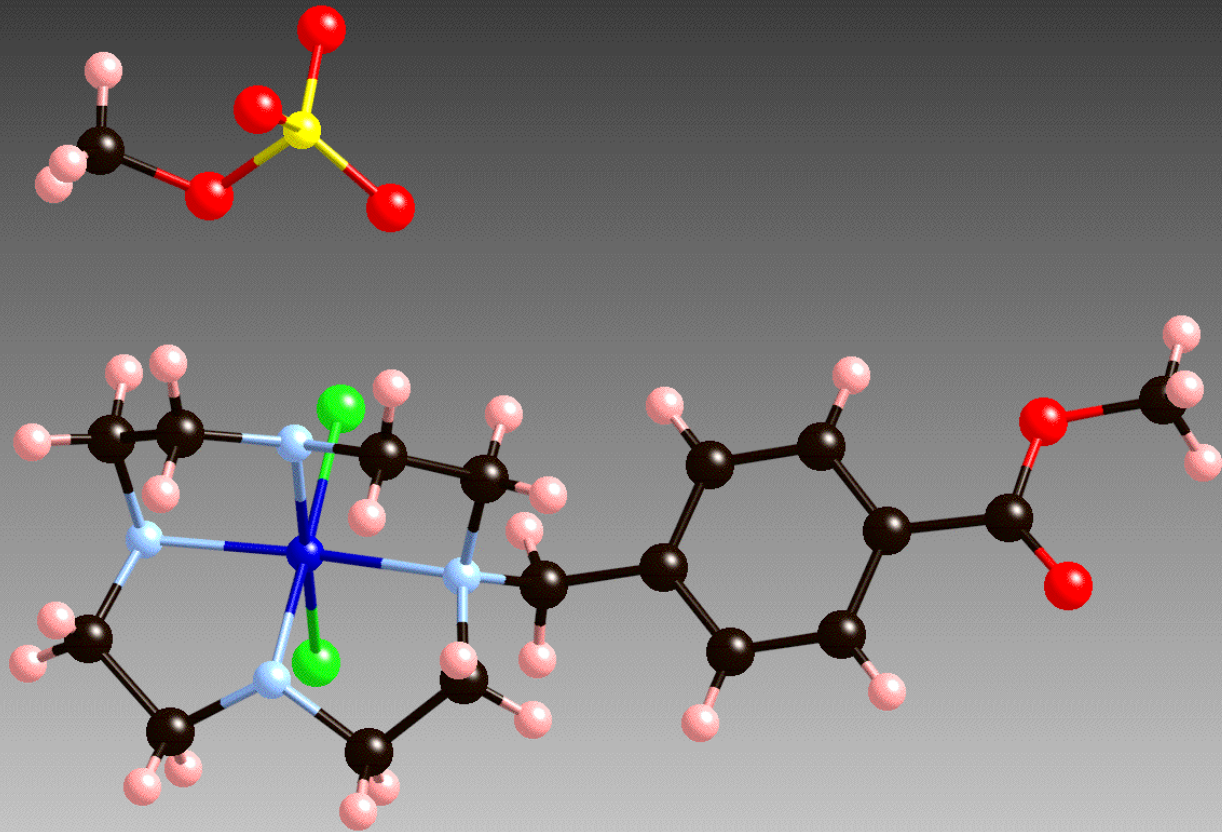
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

ESI-MS

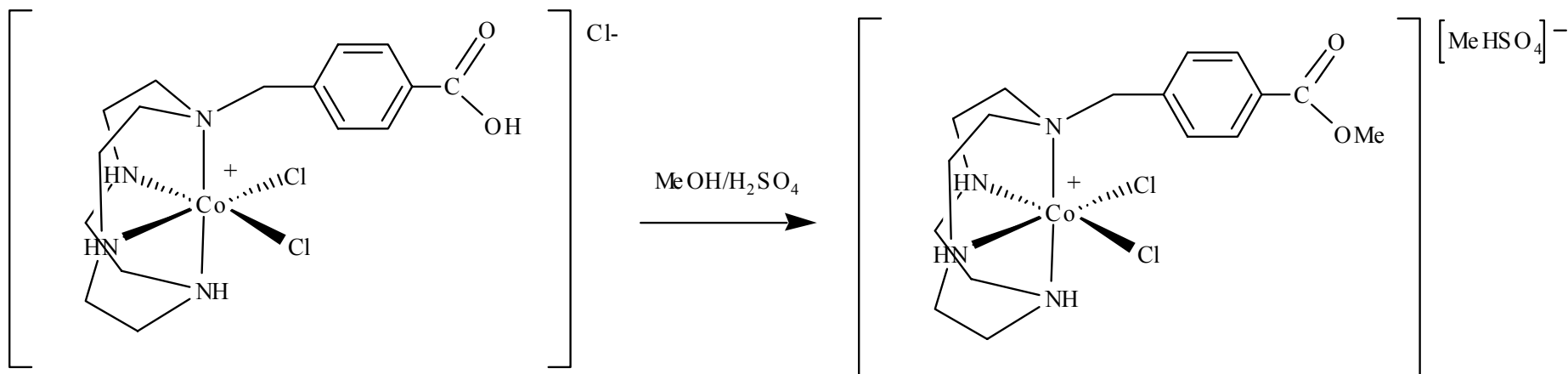
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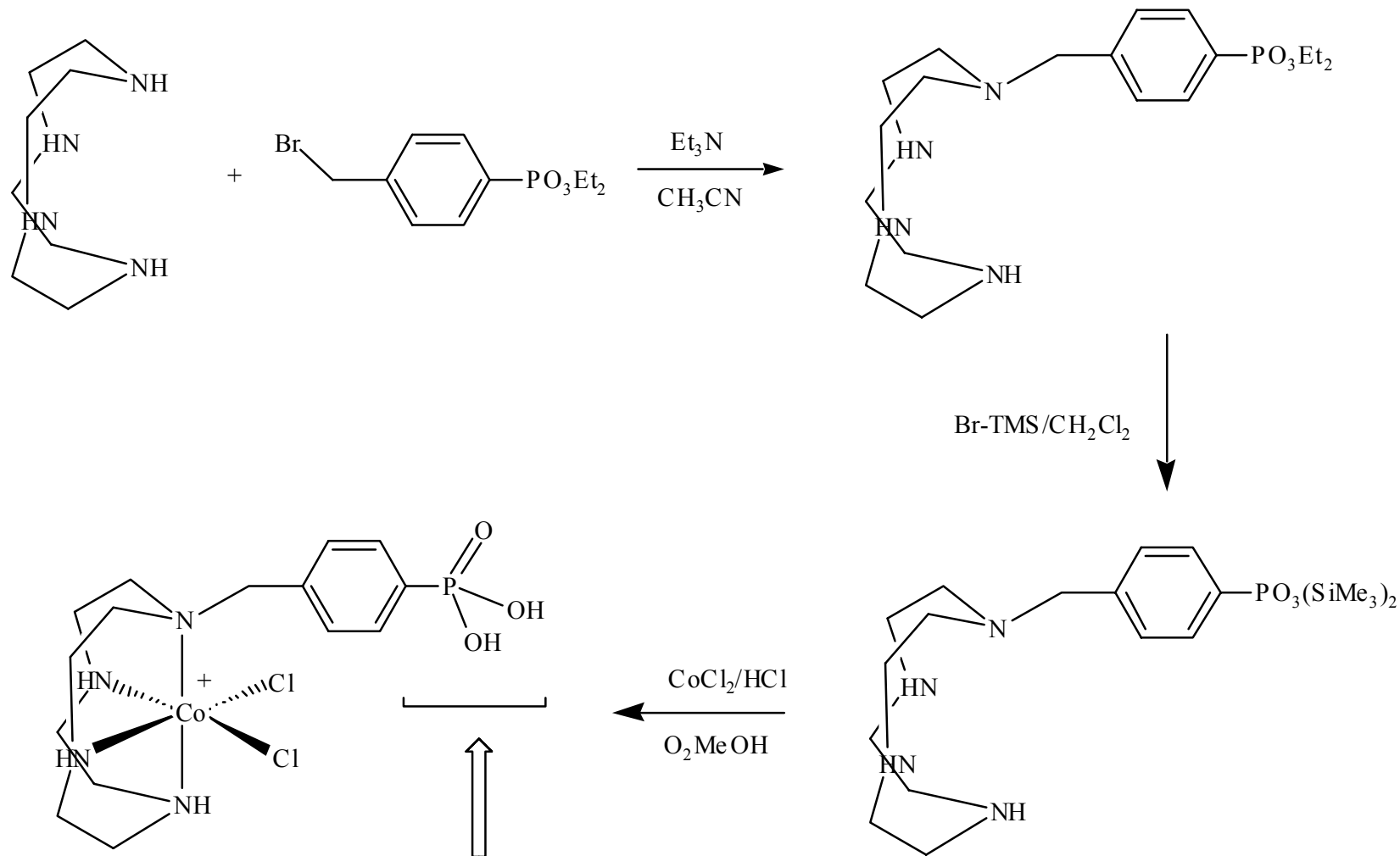
Crystal structure of cyclen methylbenzoic acid methyl ester cobalt(III) complex



Synthesis of cyclen methylbenzoic acid methyl ester cobalt(III) complex

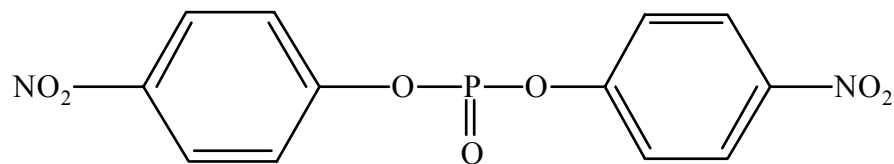


Inorganic oxide supported cobalt(III) complexes



phosphonic acid group can be
tethered to a lumina surface

Test on Model System



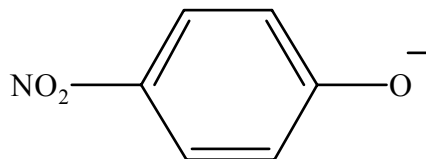
BNPP

bis nitrophenylphosphate



M-OH

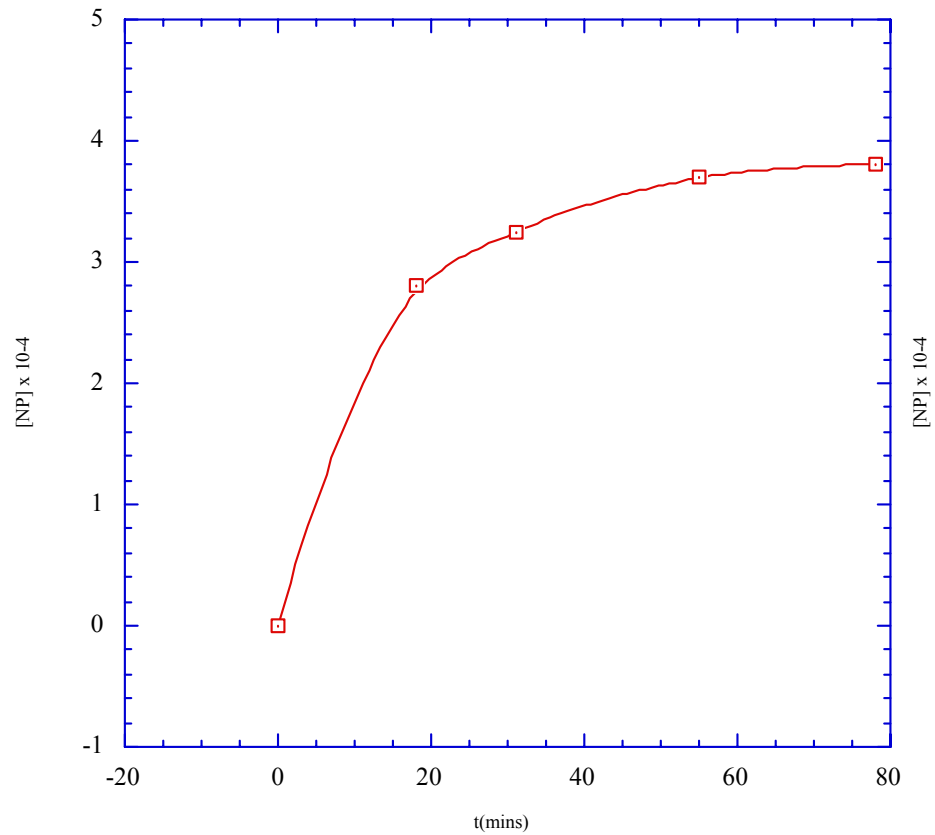
H₂O



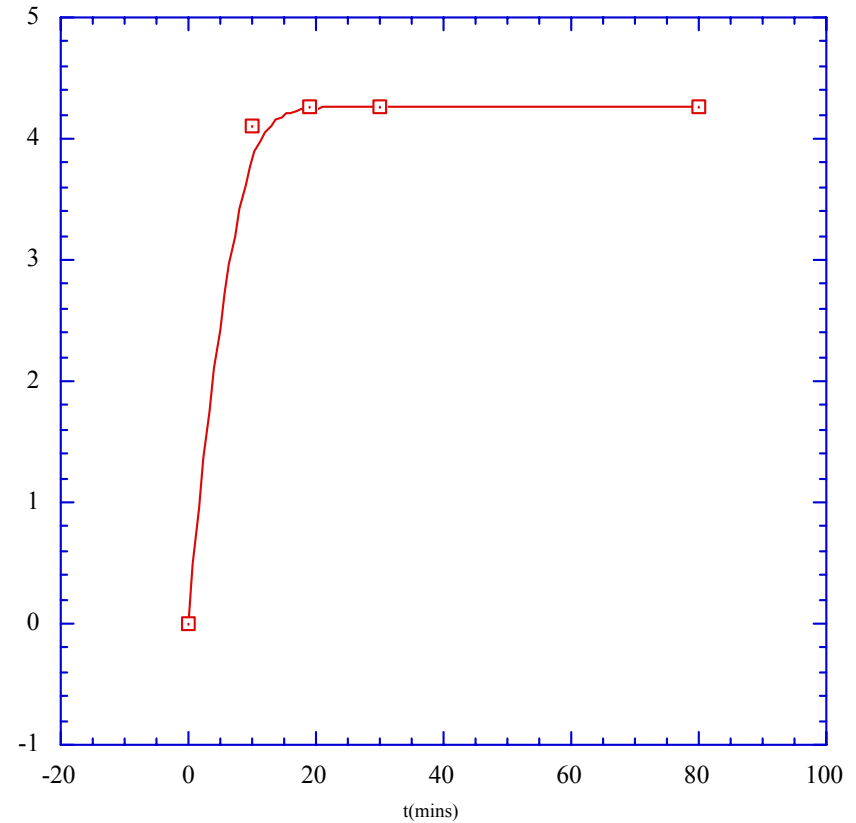
phenolate anion 400 nm

Catalysis

cat = Cocyc; cat/BNPP= 10/1; NaOH (2eq); MOPS + 15% MeOH



CoCyc/BNPPdata2



DNA Linking Schemes



Heterogenization of Catalyst on Amine-Functionalized Agarose Bead

